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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/616,560	LEDEBOER ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 12-37* is/are pending in the application.

4a) Of the above claim(s) *5-8 and 15-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,12-14,18-20 and 22-37* is/are rejected.

7)☒ Claim(s) *21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01122004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to comply*.

3.80

DETAILED ACTION

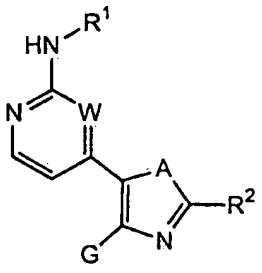
Claims 1-8 and 12-37 are pending in this application.

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on July 5, 2005 is acknowledged.

Applicant's election of the species of compound IIa-25 is acknowledged.

The species represents a compound of formula I (depicted below for convenience)



I

wherein:

W is N;

R^1 is $-T_{(n)}$-Ar^1 wherein n is 0 and Ar^1 is 3-methoxy-phenyl;

G is H;

A is –N-$T_{(n)}$-R wherein n is 0 and R is H; and

R^2 is $-Q_{(n)}$-Ar^2 wherein n is 1, Q is $-CH_2$- and Ar^2 is 2,6-dichlorophenyl.

The elected species reads on claims 1-4, 12-14 and 18-37.

Applicant is reminded of the election of species guidelines provided in MPEP § 803.02, which are followed for examination. Portion from MPEP is provided here for convenience:

> As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the non-elected species would be held withdrawn from further consideration. As in the prevailing practice, a second action on the merits on the elected claims would be final.
> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. **The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.**

The elected species was not found in the prior art search and as per the guidelines above, the examination was expanded to compounds of formula I wherein:

W is N;

R^1 is $-T_{(n)}-Ar^1$ wherein n is 0 and Ar^1 is optionally substituted phenyl;

G is H;

A is $-N-T_{(n)}-R$ wherein n is 0 and R is H or alkyl; and

R^2 is $-Q_{(n)}-Ar^2$ wherein n is 1, Q is C_{1-3} alkylidene and Ar^2 is optionally substituted phenyl,

and art was found.

Claims 5-8 and 15-17 are held withdrawn from consideration, pursuant to 37 CFR 1.142(b) as being drawn to non elected invention. All other definitions of the variables A, R^1, R^2, etc. from the generic claims 1-4, 12-14 and the species in claim 18 wherein A is other than $-N-T_{(n)}-R$ are held withdrawn from consideration, pursuant to 37 CFR 1.142(b) as being drawn to non elected subject matter.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Particularly, see Experimental example 14 in specification page 99 and page 102, which contain sequences. (See attached notice to comply).

Claim Objections

Claim 21 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claim 21 has not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 12-14, 18-20 and 22-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula (I) or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for the 'pharmaceutically acceptable derivatives' of formula (I) generally. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim recites "A compound ... or a pharmaceutically acceptable derivative thereof" wherein there is insufficient description in the specification regarding the types of 'derivatives' intended by the recitation. The recitation "pharmaceutically acceptable derivative" is explained in the specification at page 77 - 'pharmaceutically acceptable derivative means any pharmaceutically acceptable salt, ester, salt of an ester, or **other derivative** of a compound of this invention which upon administration to a recipient is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof'. However, the specification does not provide what are some of the examples of 'other derivatives', 'metabolite' or 'residue' intended by this recitation.

As explained in the specification, the recitation includes, e.g., esters of compounds of formula (I) (see page 78, lines 1-4). However, the definition of various substituent groups in formula (I) already include such groups, i.e., acids as well as esters, see e.g., the term "CO_2R"

wherein R is H, alkyl, etc. The specification does not provide what other 'compounds' of the invention are intended to be the above referred "derivatives". As explained herein, the generic formula of the claims already include both esters and the corresponding free acid forms. There is no disclosure regarding any other types of esters etc. that are capable of providing compounds of the invention. Further, specification does not provide sufficient explanation of the term "metabolite". A metabolite is any compound which is pharmaceutically active *in vivo* when it undergoes "metabolic" process and the specification does not provide any disclosure of what these compounds might be that *in vivo* transform in to the instantly claimed compounds. The specification does not provide what other 'compounds' of the invention are intended to be metabolites. Since functional groups such as esters, amides, etc. are already included in the claimed compounds, it is not clear whether compounds bearing these groups are excluded from being a potential "pharmaceutically acceptable derivatives" of the claimed invention. If compounds bearing these groups (i.e., ester, etc.), which are likely to undergo *in vivo* transformation, are excluded then what is included in the definition of the above term and where on the structural formula (I) are these groups placed; the specification does not provide any direction to one of ordinary skill in the art.

It is suggested that the recitation "pharmaceutically acceptable derivative" be replaced with -- pharmaceutically acceptable salt -- in all occurrences, throughout the claims.

Claims 22-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment of colon cancer, does not reasonably provide enablement for a method of treating or lessening severity or prevention of diseases or conditions

recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to 'a method of treating or lessening the severity of cancer, a proliferative disorder, an inflammatory disease, a neurodegenerative disease, an autoimmune disease, a condition associated with proinflammatory cytokines, infectious diseases, destructive bone disorder, an angiogenic disorder, etc.', which groups include disorders such as cancer, stroke, diabetes, Alzheimer's disease, multiple sclerosis, etc. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Test assays and procedure are provided in the specification at pages 99-108, related to measure the inhibition of JNK, Src, Lck and Aurora-2 in terms of K_i and IC_{50}. However, the disclosure does not provide how this *in vitro* test procedure correlates to the treatment of the assorted list of disorders of the instant claims. The disorders encompassed by the instant claims include neurodegenerative disorders, inflammatory disorders, autoimmune disorders, etc. some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how the patient in need of the treatment requiring the specific kinase (i.e., Aurora-2, JNK, Lck and Src) inhibiting activity is identified and further, how all types of the diseases having divers mechanisms are treated. See MPEP §

2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. Sah et al., regarding JNK pathways and mechanisms, indicate that "However, this left questions unanswered: whether activation of JNK is sufficient by itself to sensitize cells to TRAIL or there are other aspects of these translation inhibitors that contribute to the overall sensitization process" (see page 20599, col. 1).

Further, there is no disclosure regarding how the patient in need of such specific kinase inhibiting activity is identified and further, how types of proliferative, autoimmune, inflammatory, neurodegenerative, cardiovascular, infectious, etc. diseases or disorders are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. "How sister kinetochores attach to microtubules from opposite spindle poles during mitosis (bi-orientation) remains poorly understood", see Tanaka et al. (PubMed Abstract enclosed). Also, Rogers et al., express that

"How the selective release of chromosome cohesion is regulated during meiosis remains unclear". This is clearly indicative of the fact that the therapeutic role of kinase inhibitors is very speculative.

Enablement for the scope of "treating inflammatory disorder" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara,

silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

Further, neurological or neurodegenerative disorders covers diverse disorders such as Alzheimer's disease, dementia, hereditary cerebellar ataxias, paraplegias, syringomyelia, phakomatoses, and much more. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that 'some degenerative diseases are difficult to classify because they involve multiple anatomic locations' (see page 2050). For example, Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that

'[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease' (pg. 1994).

Further, the list of the diseases includes multiple sclerosis, which has traditionally been very difficult or impossible to treat effectively with chemotherapeutic agents. See e.g., Casanova et al. (PubMed Abstract enclosed) states that "Multiple Sclerosis (MS) is a disorder in which the pathogenesis is not clearly understood", see the enclosed abstract. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the "Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001" wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating or lessening the severity of a disease or disorder' solely based on the Src inhibitory activity disclosed for the compounds.

'Cardiac or cardiovascular disorders' embrace a vast array of problems, many of which are contradictory to others. Thus, it covers hypertension and hypotension. It covers various types of arrhythmias; angina pectoris', the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias, ischemic heart disease including congestive heart failure and myocardial infarction, stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCAI; elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine,

cardiomyopathy, etc. Not one compound -- let alone a genus of trillions of compounds, could possibly be effective against such disorders generally.

Stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths, behind only head disease and cancer. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

It is inconceivable as to how the claimed single class of compounds can treat infectious diseases such as viral diseases generally. For example, there is no known common therapeutic mechanism for viral diseases generally. There are more than 400 distinct viruses that infect humans producing a wide range of diseases. The Merck Manual of Diagnosis and Therapy states that "Several hundred different viruses infect humans. Because many have been only recently recognized, their clinical effects are not fully understood" and "Only a few viral diseases can be diagnosed clinically or epidemiologically" see http://www.merck.com/mrkshared/mmanual/section13/chapter162/162a.jsp. Cecil Textbook of Medicine states that "for many viral infections, no specific therapy exists. Proper use of antivirals requires specific viral diagnosis" (see the enclosed article, page 1742).

The claims recite the use of the instantly claimed compounds in treating 'angiogenic

disorders'. Angiogenesis is the process of vascularization of a tissue involving the development of new capillary blood vessels and therefore, is not seen as being a disease or disorder, but as an absolutely essential body process. Thus, there is no enablement for treating something which is not itself a problem and is indeed essential for life.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Furthermore, the scope of the method claims is not adequately enabled solely based on JNK, Src, Lck and Aurora-2 kinase inhibitory activity provided in the specification. The instant claims are drawn to 'a method treat or **prevent**...' inflammatory disease, autoimmune disease, neurodegenerative diseases including Alzheimer's disease, proliferative disease such as cancer, etc., and therefore, the instant claim language embraces disorders not only for the treatment, but for "prevention" which is not remotely enabled. The instant compounds are disclosed have p38 inhibitory activity and it is recited that the instant compounds are useful in the "prevention" of Alzheimer's disease, infections, heart attacks, etc., for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from*

happening etc. (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. The specification does not provide any disclosure regarding the prevention of the diverse disorders of the instant claims. Thus, it is inconceivable as to how the claimed compounds can not only treat but also "prevent" a myriad of diseases with different etiologies. For example, a neurodegenerative disease such as Alzheimer's disease has no known cause and has been treated mostly by choline esterase inhibitors to prolong the activity of acetylcholine. A disease such as myocardial ischemia mostly relates to the deposition of plague in the coronary artery. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 12-14, 18-20 and 22-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 1, in the definition of Ar^2, the term "saturated" is repeated, see page 3, lines 24 and 26 (portion of the claim depicted below for convenience).

> Ar^2 is selected from a 3-7 membered monocyclic saturated, saturated or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 8-10 membered bicyclic saturated, saturated or aromatic ring having 0-5 heteroatoms independently selected

2. In claim 1, in the proviso, the recitation "W is nitrogen" is redundant because W is always nitrogen in the claim.
3. Claim 18 recites "selected from those listed in Tables 1-3" without providing the claimed compounds. A claim must include all limitations within the claim or should refer to another claim having the limitation.
4. Claim 19 depends from 'any one of claims 1 to 18', which includes the canceled claims 9-11. Appropriate correction is required.

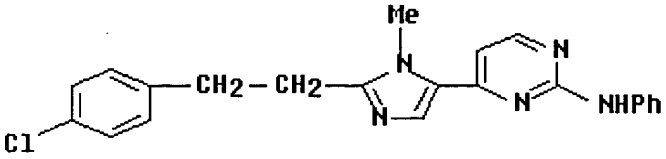
Claim Rejections - 35 USC § 102

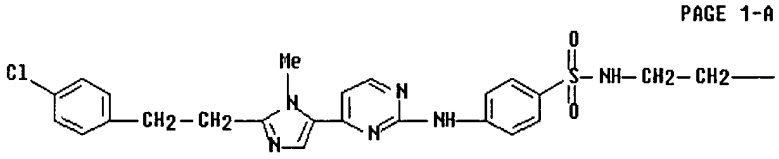
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 19-20 and 22-37 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 03/076434 (effective date March 6, 2003). The instant claims read on reference disclosed compounds, see formula (I) and the corresponding species disclosed in page 69, method 102 and page 74, method 116 (the structural formulae depicted below for convenience):





PAGE 1-B

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Note: Applicant's claim for domestic priority under 35 U.S.C. 119(e) over U.S. Provisional Application No. 60/395,202 filed July 9, 2002 is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims of this application. Particularly, the provisional application does not support the definition of variables G and Q. The instant claims define G and Q as follows:

G is hydrogen or C_{1-3} aliphatic wherein one methylene unit of G is optionally replaced by –C(O)-, -C(O)O-, -C(O)NH-, $-SO_2-$, or $-SO_2NH-$;

Q is a C_{1-3} alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally replaced by –C(O)-, -C(O)O-, -C(O)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)N(R)-, -N(R)N(R)C(O)-, -N(R)C(O)-, -N(R)C(O)O-, -N(R)C(O)N(R)-, -S(O)-, $-SO_2-$, $-N(R)SO_2-$, $-SO_2N(R)-$, $-N(R)SO_2N(R)-$, -O-, -S-, or –N(R)-;

Provisional application 60/395,202 provides:

"G is hydrogen or C_{1-3} aliphatic" (see page 9, line 4) and

"Q is a C1-3 alkylidene chain" (see page 11, line 4).

Therefore, there is no support for the recitation '... methylene units being optionally replaced by –C(O)-, -C(O)O-, ...'. Accordingly, the instant claims are entitled to the filing date of July 9, 2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 12-14, 18-20 and 22-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newcombe et al., WO 03/076434. The reference teaches a generic group of imidazolyl substituted pyrimidine compounds, which embraces applicant's instantly claimed compounds. See formula (I) in page 2, and the compounds thereof in the examples and preparation methods. The compounds are taught to be useful as pharmaceutical agents having kinase inhibitory activity, see page 1, lines 27+. Claims 1-2, 19-20 and 22-37 read on reference disclosed compounds as explained under 35 U.S.C 102(e) rejection above. The remaining claims differ from the reference by reciting specific species or a more limited subgenus than the reference. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Alternatively, claim 3 recites the limitation R^2 is $-CH_2-Ar_2$ as compared to the reference compounds 102 and 116 wherein the imidazolyl has a $-CH_2-CH_2$-4-chlorophenyl in the analogous position. Therefore, the instantly claimed compounds differ from the reference compounds by a $-CH_2-$ group and it is well established that compounds that differ by a $-CH_2-$ group are structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

Claims 1-2, 19-20, 23-25 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hongu et al., WO 02/083111. The reference teaches imidazolyl compounds that are structurally analogous to instantly claimed compounds. See the generic structural formula (I) in page 3 and the corresponding species of Example no. 100 disclosed in page 63, Table 8. The compounds are taught to be useful as pharmaceutical therapeutic agents, see page 286. The instant compounds differ from the reference compounds by having the pyrimidine attached through a position different from the reference compounds. The instant compounds have the 4-position of the pyrimidine as the point of attachment to the imidazolyl whereas the reference compound 100 is attached at the 5-position of the pyrimidine and therefore, the instantly claimed compounds are positional isomers of the reference compounds. It would have

been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are positional isomers of the reference compounds. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such isomeric compounds are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds, i.e., as pharmaceutical agents. It has been held that a compound, which is structurally isomeric with a compound of prior art is prima facie obvious absent unexpected results. *In re Finley*, 81 USPQ 383 (CCPA 1949); *In re Norris*, 84 USPQ 458 (CCPA 1950); *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990).

Receipt is acknowledged of the Information Disclosure Statement filed on January 12, 2004 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Acting-SPE of 1624, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

September 6, 2005

NOTICE TO COMPLY	Application/Control No.	Applicant(s)	
	10/616,560	LEDEBOER et al	
	Examiner	Art Unit	
	Rao, D.	1624	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: .

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510
For CRF Submission Help, call (571) 272-2501/2583.
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